

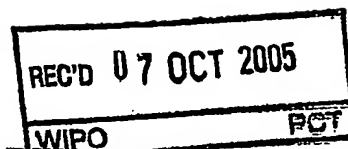
PATENT COOPERATION TREATY



PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference 17165 KB	FOR FURTHER ACTION See Form PCT/PEA/416	
International application No. PCT/HU2004/000070	International filing date (day/month/year) 30.06.2004	Priority date (day/month/year) 02.07.2003
International Patent Classification (IPC) or national classification and IPC C07D495/04		
Applicant EGIS GYOGYSZERGYAR RT.		
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau) a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>		
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>		
Date of submission of the demand 02.02.2005	Date of completion of this report 06.10.2005	
Name and mailing address of the International preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Baston, E Telephone No. +49 89 2399-8229 	

**INTERNATIONAL PRELIMINARY REPORT
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International application No.
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Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-20 as originally filed

Claims, Numbers

1-11 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-11
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-11
Industrial applicability (IA)	Yes: Claims	1-11
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

To section V

The following documents were cited in the search report and were considered for the examination of the present application:

- D1: WO 03/051362 A (AVHAR-MAYDAN SHARON ; TEVA PHARMA (IL); WIZEL SHLOMIT (IL); KOVALEVSKI) 26 June 2003;
- D2: WO 99/65915 A (SANOFI SYNTHELABO ; BOUSQUET ANDRE (FR); CASTRO BERTRAND (FR); SAINT G) 23 December 1999;
- D3: EP-A-0 281 459 (SANOFI SA) 7 September 1988;
- D4: CAIRA M R: "CRYSTALLINE POLYMORPHISM OF ORGANIC COMPOUNDS" 1998, TOPICS IN CURRENT CHEMISTRY, SPRINGER, BERLIN, DE, PAGE(S) 163-208.

The present application is directed to a process for the preparation of polymorph form I of Clopidogrel hydrogensulfate. This compound (D3) and its polymorphs I (D1) and II (D2) are known from the prior art. The process consists in either using two solvents A and B consecutively or employing a mixture of solvents A and B. In both cases polymorph form I is added to the mixture.

D1 also specifies a process for the preparation of polymorph I, but it can be distinguished from the claimed one by the fact that no pure polymorph I is added. Thus the claimed subject-matter is considered novel (Art. 33(2) PCT).

The description states that applying a procedure as stated in D1 would not result in pure polymorph I, but mostly leads to mixtures with the presence of amorphous material. In this context it has to be stated that D1 indeed discloses preparation procedures which result in pure polymorph I and also using a two solvent system. Thus a possible superiority of the claimed procedure can only be ascribed to the fact that pure polymorph I is added to the mixture. However, in view of general knowledge with respect to crystal engineering (compare D4, page 200, chapt. 4.2) the use of seed crystals is considered a routine operation and cannot represent an inventive contribution over D1.

In reply to these arguments the applicant stressed that the claimed process is characterized by the combined use of specific solvents and seed crystals. Not necessarily would the use of seed crystals result in the formation of polymorph 1 (compare table 1). However, it has to be considered that general expressions like solvent A and solvent B

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(SEPARATE SHEET)**

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extend the scope of protection to those solvents which cannot be used for the claimed process. The arguments provided by the applicant confirm that the choice of the solvents has to be done very carefully. The involvement of an inventive step is not acknowledged (Art. 33(2) PCT).

Claim 4 is not clear (Art. 6 PCT) due to the expression "lower alkyl".